PHARMACOKINETICS
(TRANSPORT & ABSORPTION)

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M. Phil (pharmacology)
PhD(1)

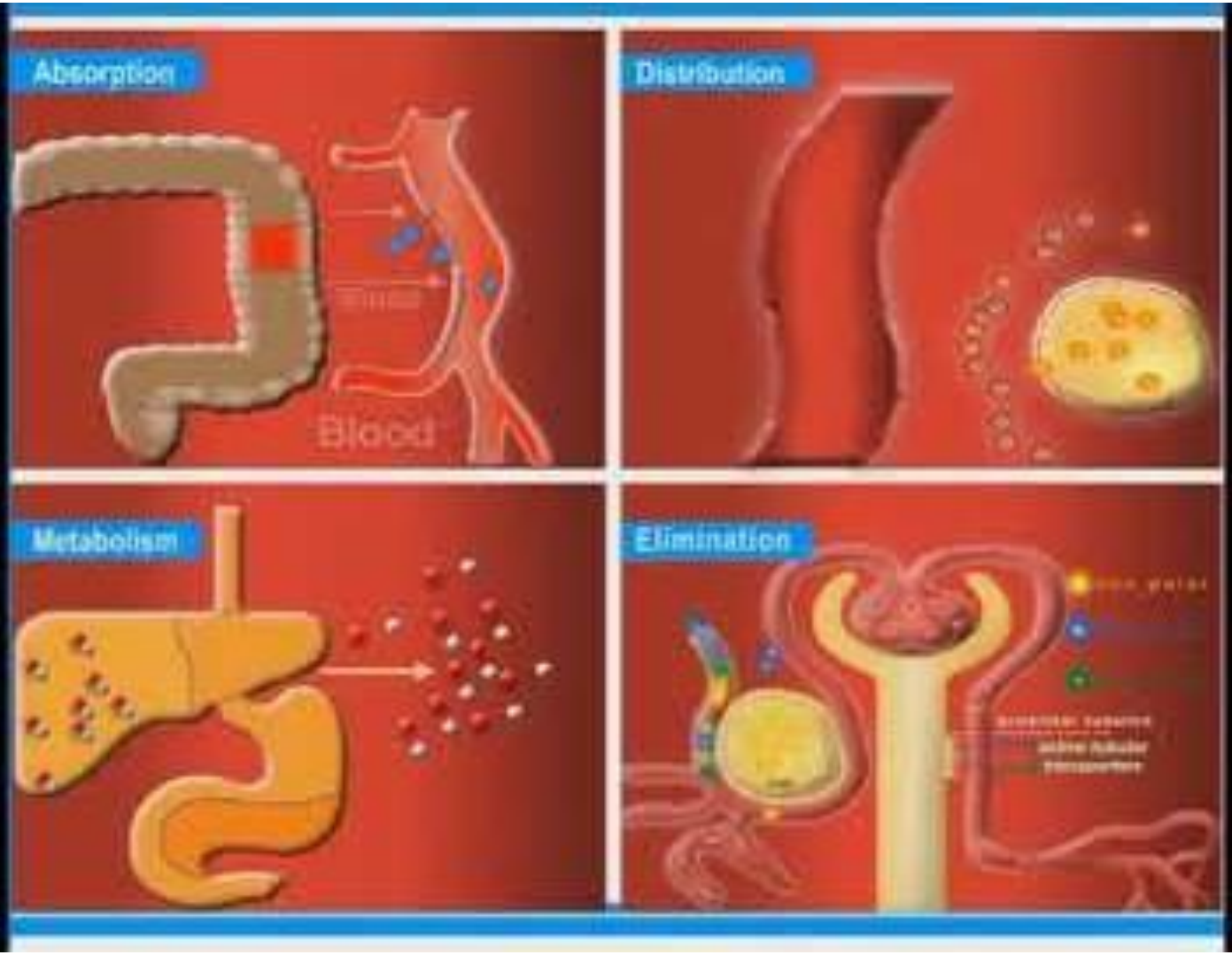
Learning outcomes

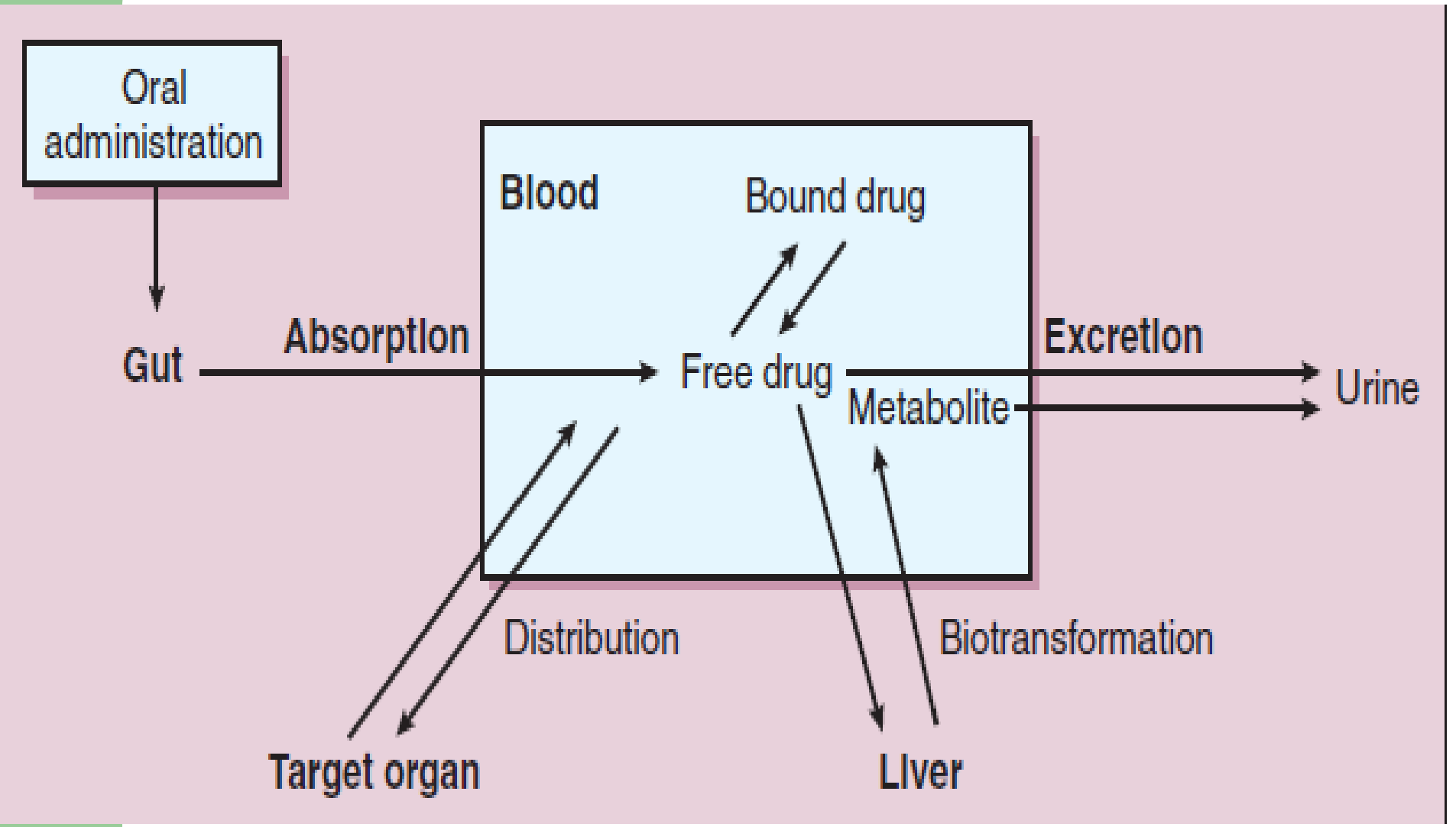
- Define absorption, permeation
- Means of transport of drugs
- Factors modifying absorption of drugs
- Effect of ionization (Henderson hasselbalch equation)
- Ion trapping and its significance
- Bioavailability, factors
- Bioequivalence and therapeutic equivalence

Pharmacokinetics:

(Greek : Kinesis – movement)

It is the branch of pharmacology which deals with the quantitative study of absorption, distribution, binding / storage, biotransformation & excretion of drugs. Together with dose of drugs these parameters determine the onset, intensity & duration of action.

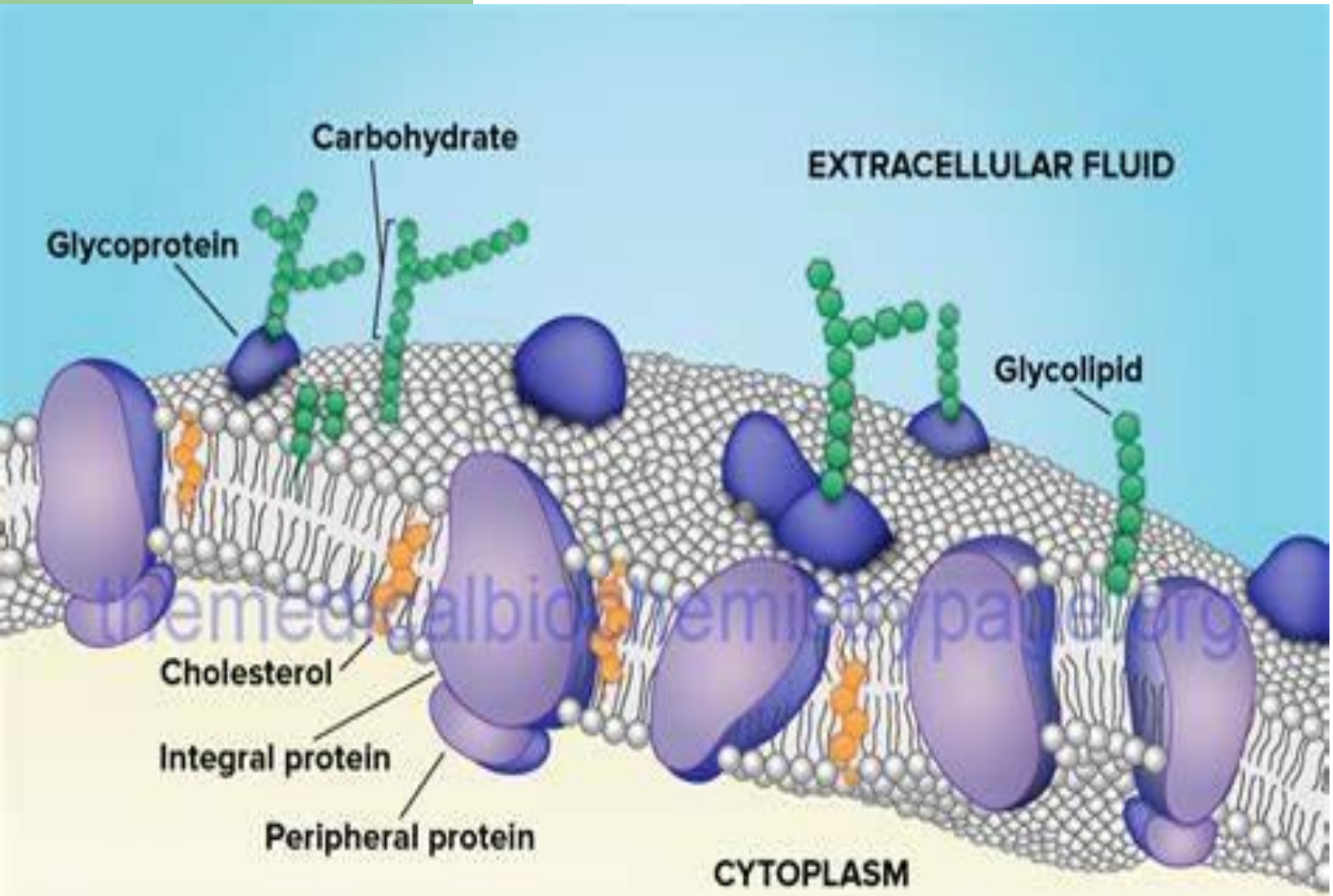

Absorption
Blood
Distribution
Metabolism
Elimination


Oral administration
Blood
Bound drug
Gut
Absorption
Free drug
Excretion
Urine
Metabolite
Distribution
Biotransformation
Target organ
Liver

PASSAGE OF A DRUG THROUGH BIOLOGICAL MEMBRANE

PERMEATION

- It is the movement of drug molecules into and within the biological environment.


Carbohydrate
EXTRACELLULAR FLUID
Glycoprotein
Glycolipid
Cholesterol
Integral protein
Peripheral protein
CYTOPLASM

- Simple Transport
  - Simple diffusion
  - Filtration

- Facilitated Transport
  - Active transport
  - Facilitated diffusion

  - Others (pinocytosis)

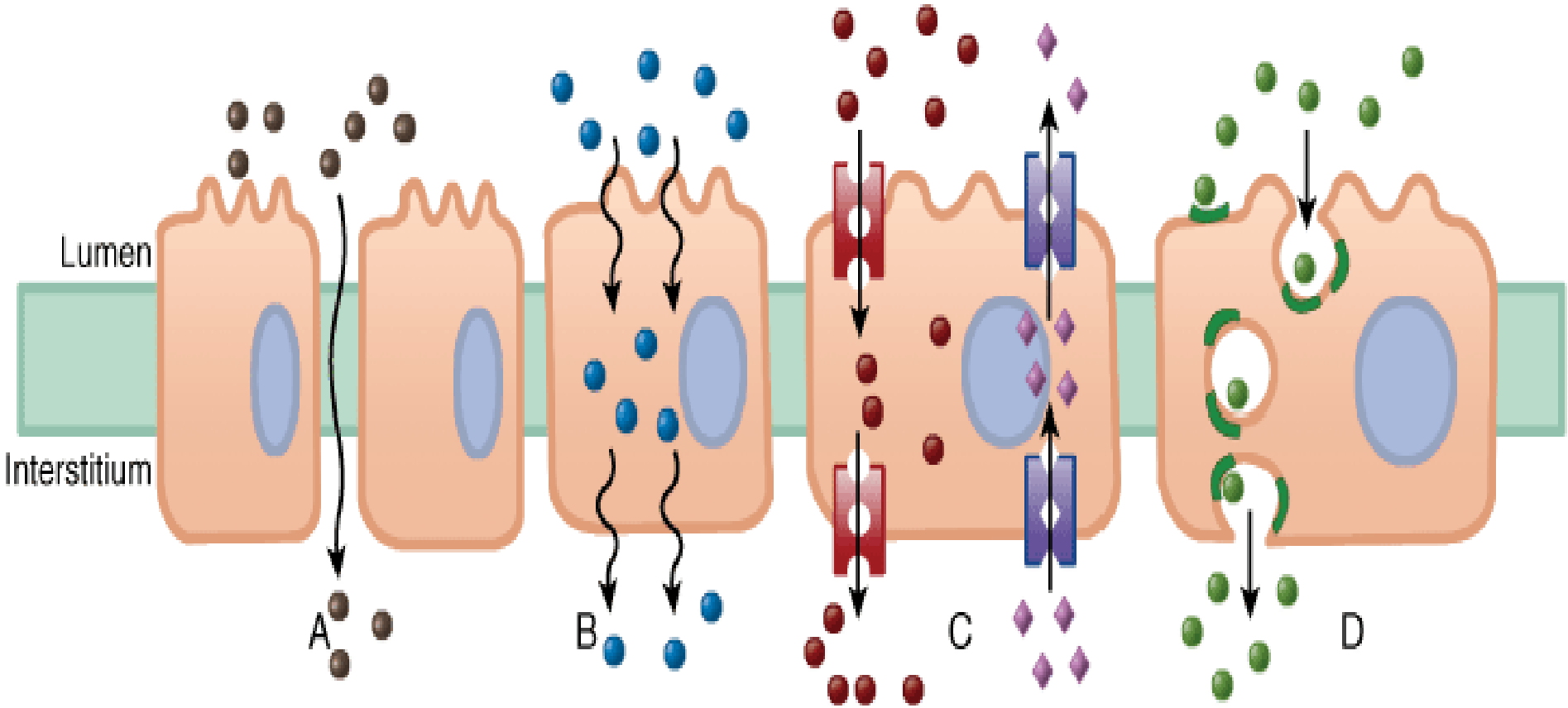

Lumen
Interstitium
A
B
C
D

Table 1–2 Some Transport Molecules Important in Pharmacology.

Transporter	Physiologic Function	Pharmacologic Significance
NET	Norepinephrine reuptake from synapse	Target of cocaine and some tricyclic antidepressants
SERT	Serotonin reuptake from synapse	Target of selective serotonin reuptake inhibitors and some tricyclic antidepressants
VMAT	Transport of dopamine and norepinephrine into adrenergic vesicles in nerve endings	Target of reserpine
MDR1	Transport of many xenobiotics out of cells	Increased expression confers resistance to certain anticancer drugs; inhibition increases blood levels of digoxin
MRP1	Leukotriene secretion	Confers resistance to certain anticancer and antifungal drugs

MDR1, multidrug resistance protein-1; MRP1, multidrug resistance-associated protein 1; NET, norepinephrine transporter; SERT, serotonin reuptake transporter; VMAT, vesicular monoamine transporter.

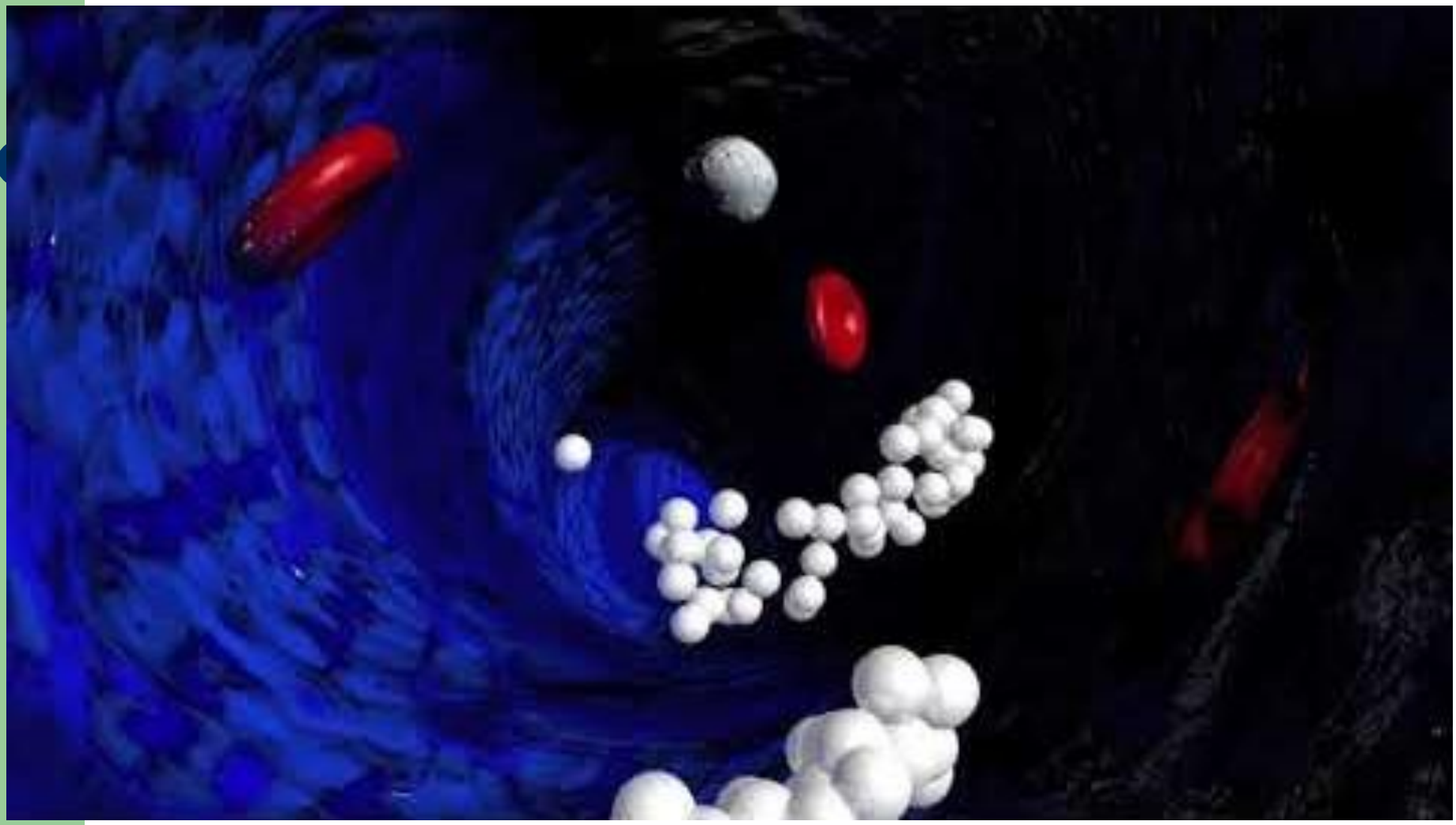
P Glycoproteins

- ??????
- Students assignment
- What is Pgp, ABC, Pgp related drugs
- How does Pgp act…
- Prodrug

Absorption

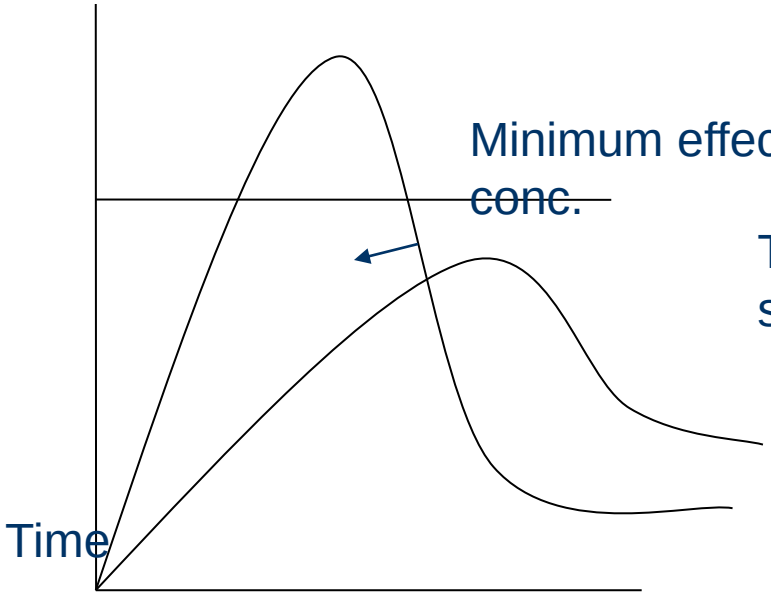
Passage of Drugs from site of Administration to the Systemic Circulation

One of the Pharmacokinetic Processes



Therapeutic success of a rapidly & completely absorbed drug.

→Not only the magnitude of drug that comes into the systemic circulation but also the rate at which it is absorbed is important this is clear from the figure.



Factors Affecting Rate and Extent of Absorption

A. **Drug Related Factors**

B. **Patient Related Factors**

Drug Related Factors

- Lipid Solubility
- Degree of Ionization
- Concentration of Drug
- Physical State
- Molecular Size

- Dosage Form
- particle size
- disintegration time (rate of breakup)
- dissolution rate (rate at which it goes into solution

Lipid Solubility or Lipid Aqueous Partition Coefficient

- Measure of how readily a drug enters the lipid medium from an aqueous medium.

- Flux = (C1-C2) x

$$\frac{\text{Area x Permeability Co-efficient}}{\text{Thickness}}$$

Drug solubility

It affects the extent of absorption:

- **Highly lipid soluble drugs with some water solubility** are absorbed to a better extent. e.g. Diazepam ---- 90%.

Some degree of water solubility is essential to cross the water layer adjacent to cells of the epithelial lining of gut.

- **Less lipid soluble / hydrophilic drugs** are absorbed to lesser extent. e.g. Atenolol ---- 56%

- **Extremely lipid soluble / Lipophilic drug** is not soluble enough to cross the water layer adjacent to the cell , less abs. e.g. Acyclovir -- only 23% .

Degree of Ionization

- The extent to which a drug becomes ionized depends on the pH of the Medium and the pKa of the drug
- Acidic drugs remain mostly unionized in the acidic medium (stomach)

- **Basic drugs remain mostly unionized in the alkaline medium (intestine)**
- **Some drugs remain highly ionized**

  a) Negatively charged : Heparin

  b) Positively charged: Tubocurarine & Suxamethonium

- Some drugs do not ionize & remain in unionized form-for example digoxin and chloramphenicol

- **Not charged but lipid insoluble due to their structure** **---**
  Aminoglycosides(Streptomycin)---

i. Dosage forms :

- **Liquid preparation** are better absorbed than **solids** ---tablets, capsules.

- The tablets require disintegration,& it must dissolve in the aqueous biophase before the drug is absorbed.
- Liquid preparation may be in suspension or solution form.

The solutions are better absorbed

Slow release preparations---they are specially formulated to delay absorption.

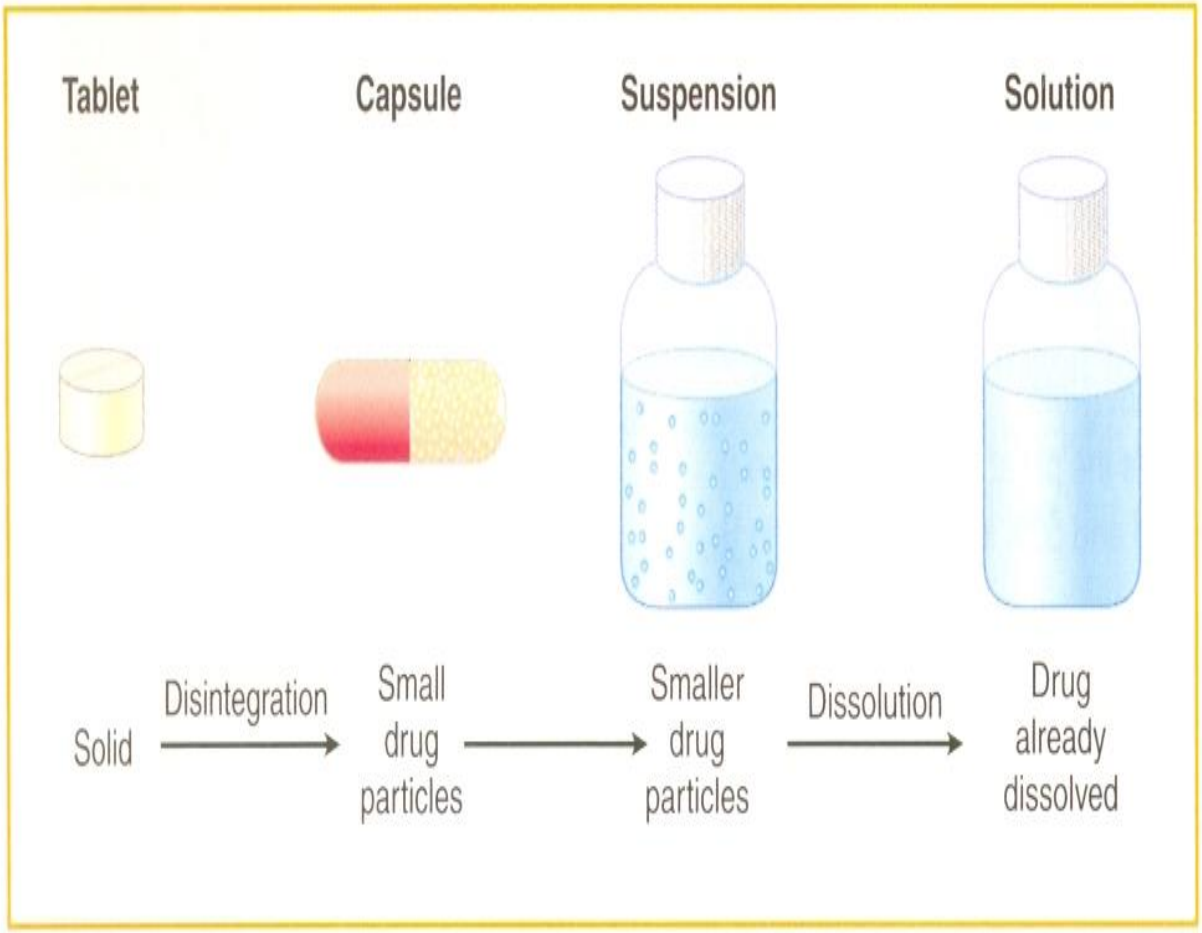
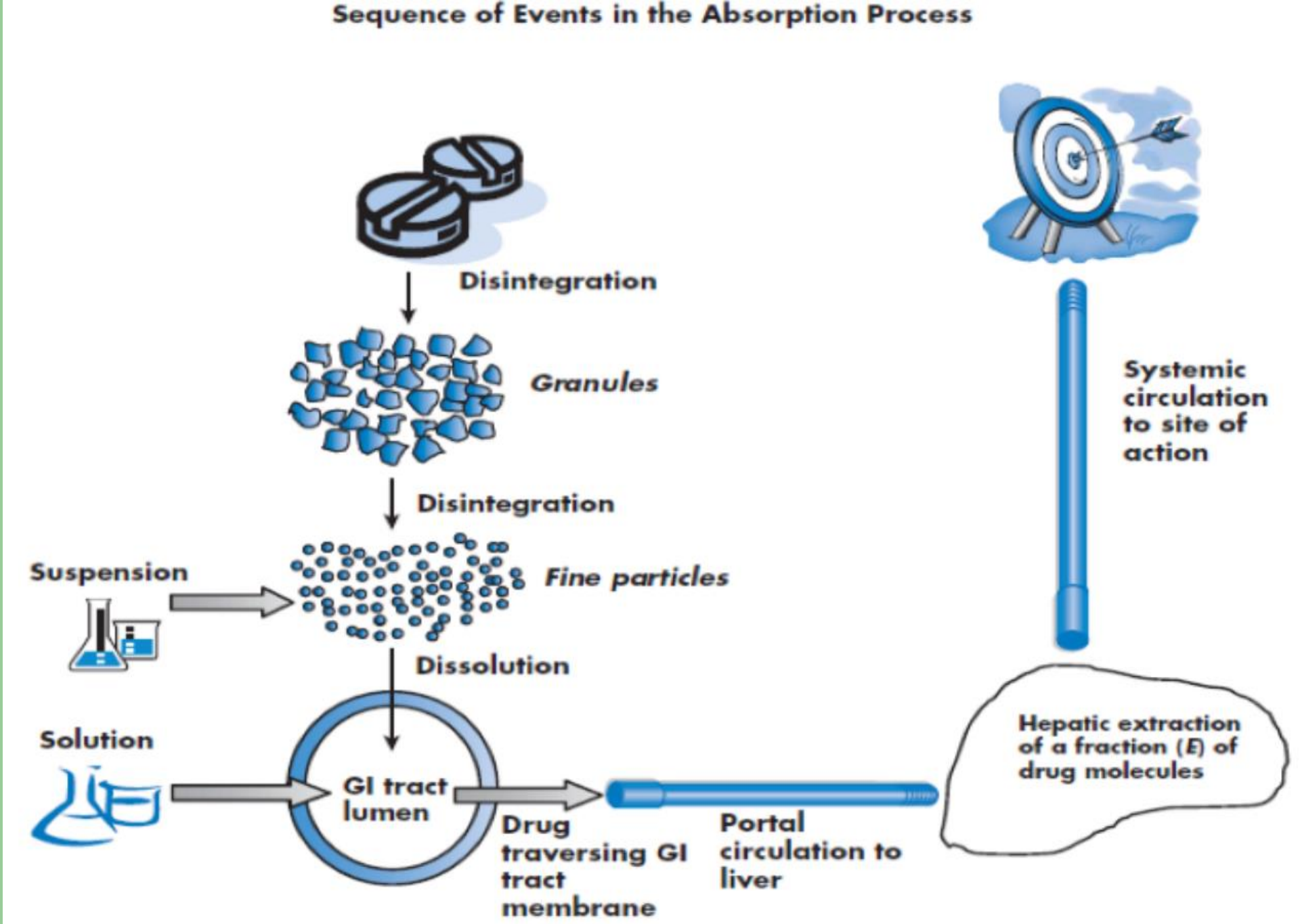


Figure 1-1. Disintegration and dissolution characteristics of various dosage forms.



Sequence of events in the absorption process GI, Gastrointestinal

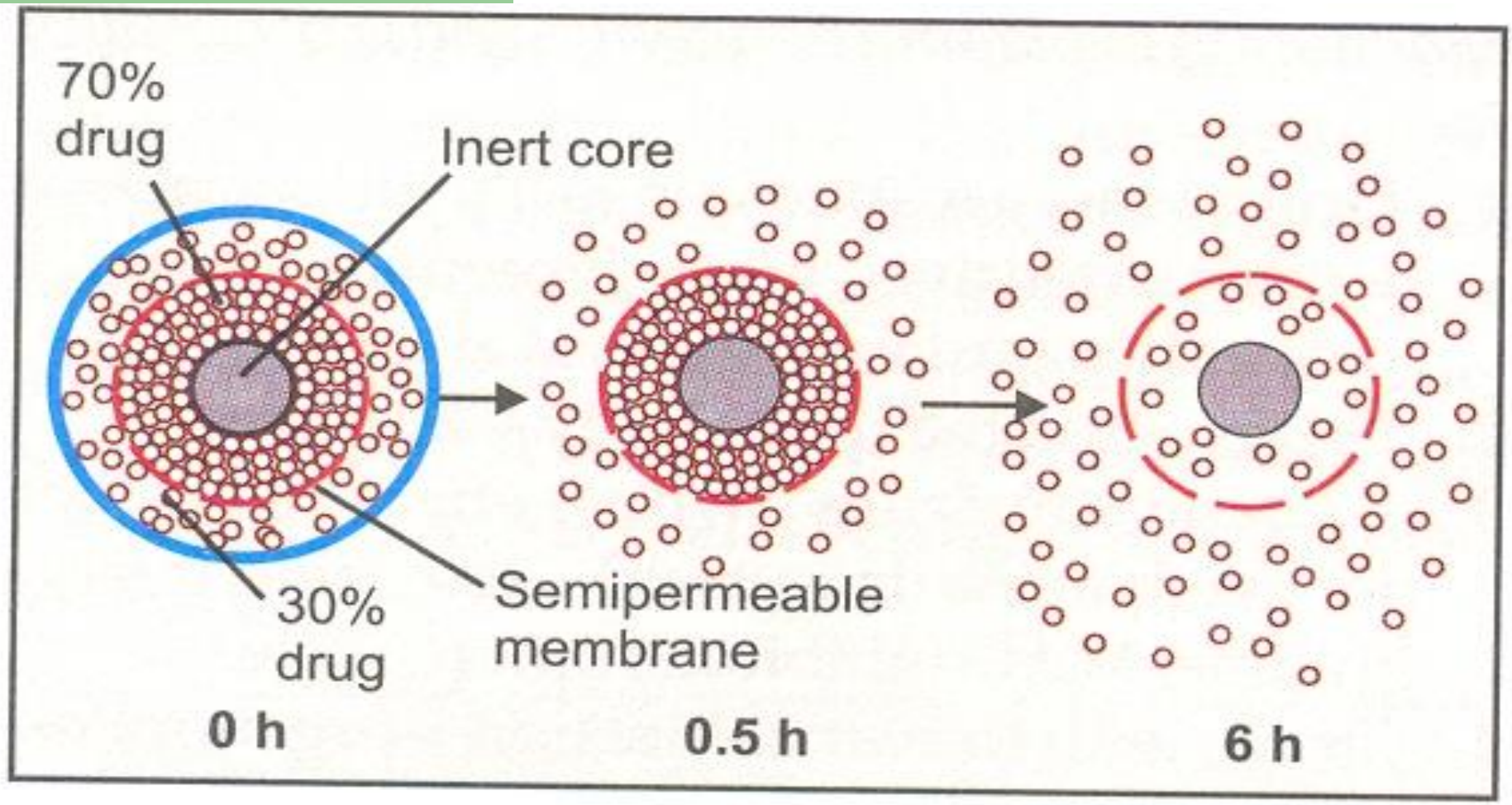


Fig. 2.13: Pattern of drug release from oral controlled release tablet/capsule; 30% of the dose outside the semipermeable membrane is released immediately, while 70% of the dose is released slowly through the membrane over the next 4-8 hours.

Patient Based Factors

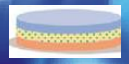
- Route of Administration
- pH of the Absorbing Surface
- Surface Area of Absorption
- Thickness of Diffusing Path
- Vascularity of Absorbing Surface

Routes of Drug Delivery

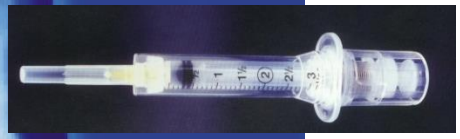
Parenteral (IV)

Inhaled

Oral



Transdermal



Parenteral (SC, IM)

Topical

Rectal

Absorption from GIT

- Site and pH
- Presence of Food
- GIT Motility
- Presence of Other Drugs
- Metabolism
- GIT Disease
- P-Glycoproteins

Site of absorption

- Mainly small intestine
- Reason?

- Structural and functional integrity

Presence of Food

- Generally most drugs are absorbed better on an empty stomach
- Presence of food dilutes the drug and retards absorption
- Food delays gastric emptying
- Certain drugs form poorly absorbed complexes with food constituents e.g. tetracyclines with calcium in milk

- Better absorption?

GIT Motility (GIT Transit time)

- Increased GIT motility as seen in diarrhea and by certain drugs decreases GIT transit time and thus decreases absorption
- Delayed gastric emptying decreases absorption and vice versa (from intestine)

Metabolism/Destruction

Rapid degradation (metabolism) of the drug in the GIT decreases absorption

Penicillin G is destroyed by acid

Insulin by peptidases and thus ineffective orally

Enteric coating of some drugs can prevent this

Bacterial metabolism

- Digoxin.30%

- If broad spectrum antibiotics are given, they can kill the normal flora:
- absorption of Digoxin.
- disturb the entero-hepatic circulation of oral contraceptives..consequence

GIT disease

- **Malabsorption : Tropical sprue, Ulcerative Colitis**
- **Diarrhea**
- **Obstruction in GIT tract including Intestinal Obstruction**

Presence of Other Drugs

- **Formation of insoluble complexes e.g. Tetracyclines with Iron preparations and antacids,**
- **Vitamin C and iron**
- “ Vit.K is ↓ by liquid paraffin
- **Some drugs may alter GIT motility**
- **Some drugs may cause mucosal damage**

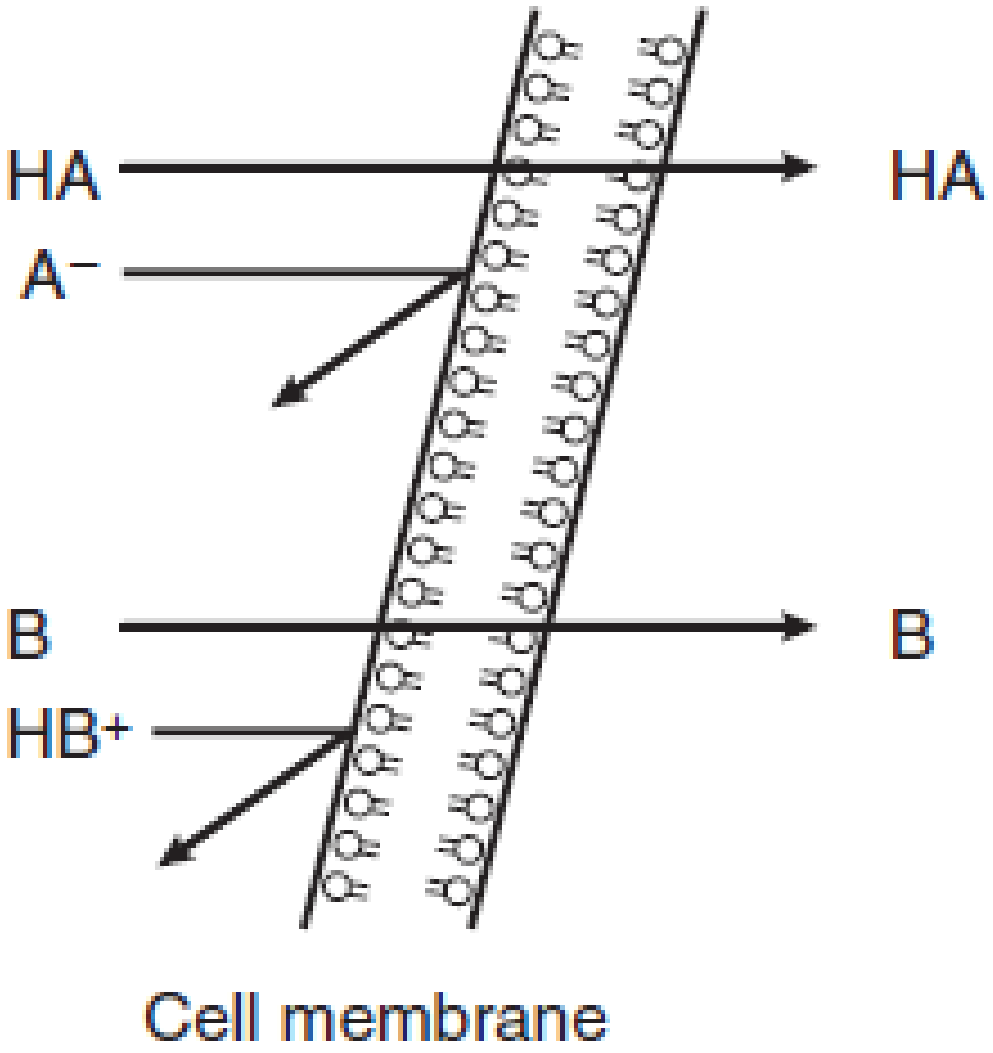
Effect of pH on the absorption of weak acids and weak bases

-many drugs are weak acids or weak bases

for weak acids the protonated form is nonionized

for weak bases the unprotonated form is nonionized

i.e. the red form goes across biomembranes


HA
HA
A⁻
B
B
HB⁺
Cell membrane

- **Thus :**

  HA and B are unionized

  HB+ and A- are ionized

Henderson Hasselbalch Equation

$$pH = pK_a + \log \frac{\text{unprotonated}}{\text{Protonated}}$$

For Acid

$$pH = pK_a + \log \frac{A^- \text{ (Ionized)}}{HA \text{ (Non-ionized)}}$$

For Base

$$pH = pK_a + \log \frac{B \text{ (Non-ionized)}}{BH^+ \text{ (Ionized)}}$$

Dissociation Constant and pKa

The Ka is the dissociation constant and pKa is the negative logarithm of the dissociation constant of the weak electrolyte.

- **pKa is a measure of the strength of interaction of a compound with a proton**

  The less the interaction the lower the pKa

- **Since acids have tendency to donate proton and thus have less interaction, they have lower pKa**

Example

- If pH = pKa

- $pH = pKa + \log \frac{\text{ionized}}{\text{un- ionized}}$

$pH - pKa = \log \frac{\text{ionized}}{\text{un- ionized}}$

$\text{thus } 0 = \log \frac{\text{ionized}}{\text{un- ionized}}$

- **Log (?) = 0**
- **Log (1) = 0**
- **Thus $\frac{\text{Ionized}}{\text{Unionized}}$ =1**

Thus 50% of drug is ionized and 50% is unionized

- **Thus pKa is numerically equal to the pH at which the drug is 50 % ionized AND 50% unionized**

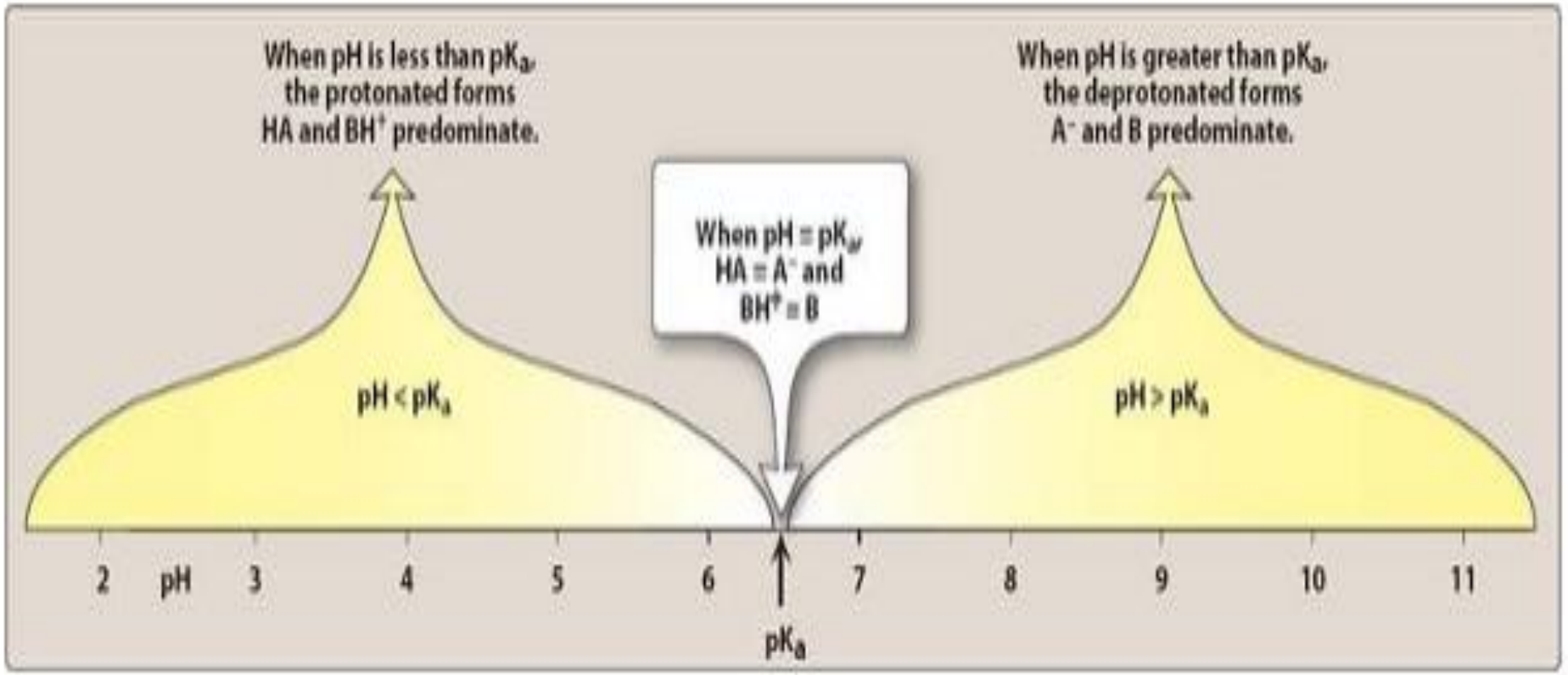
- **If an acidic drug of pKa 3.5 (aspirin) is put in the medium of pH 3.5, 50% of the drug would be in the ionized form.**

- From the Henderson Hasselbalch equation:

  When pH is less than pKa,

  the Protonated forms HA (unionized form) and BH+ (ionized form) dominate

And when pH is greater than pKa, unprotonated forms A- (ionized) and B (un-ionized) dominate


When pH is less than pK_a, the protonated forms HA and BH^+ predominate.
When pH is greater than pK_a, the deprotonated forms A^- and B predominate.
When $pH = pK_a$, $HA = A^-$ and $BH^+ = B$
$pH < pK_a$
$pH > pK_a$
2
pH
3
4
5
6
7
8
9
10
11
pK_a

We can also conclude that an acidic drug will be MORE unionized in an ACIDIC medium and thus better absorbed

And basic drug will be ionized in an acidic medium and will be less absorbed

Because When pH is less than pKa, the Protonated forms HA (unionized form) and HB+ (ionized) dominate

Ion Trapping

- The unionized form of acidic drugs that cross the surface membrane of gastric mucosal cell reverts to ionized form within the cell (pH 7) and thus slowly passes on to the ECF
- Thus it become trapped in the cell.
- “A weak electrolyte crossing a membrane to encounter a pH from which it cannot escape easily”
- Other sites: Breast milk, aqueous humor, prostatic and vaginal secretions

Application

- Acidic drugs are ionized more in alkaline urine,
- Therefore do not diffuse back into the kidney tubules and are excreted faster
- So if some person has taken excess acidic drug, we can make the urine alkaline to INCREASE the excretion of the acid

Definition of Bioavailability

" The fraction of unchanged drug reaching the systemic circulation following administration by any route"

Given in Percentage

Rate of bioavailability is also important

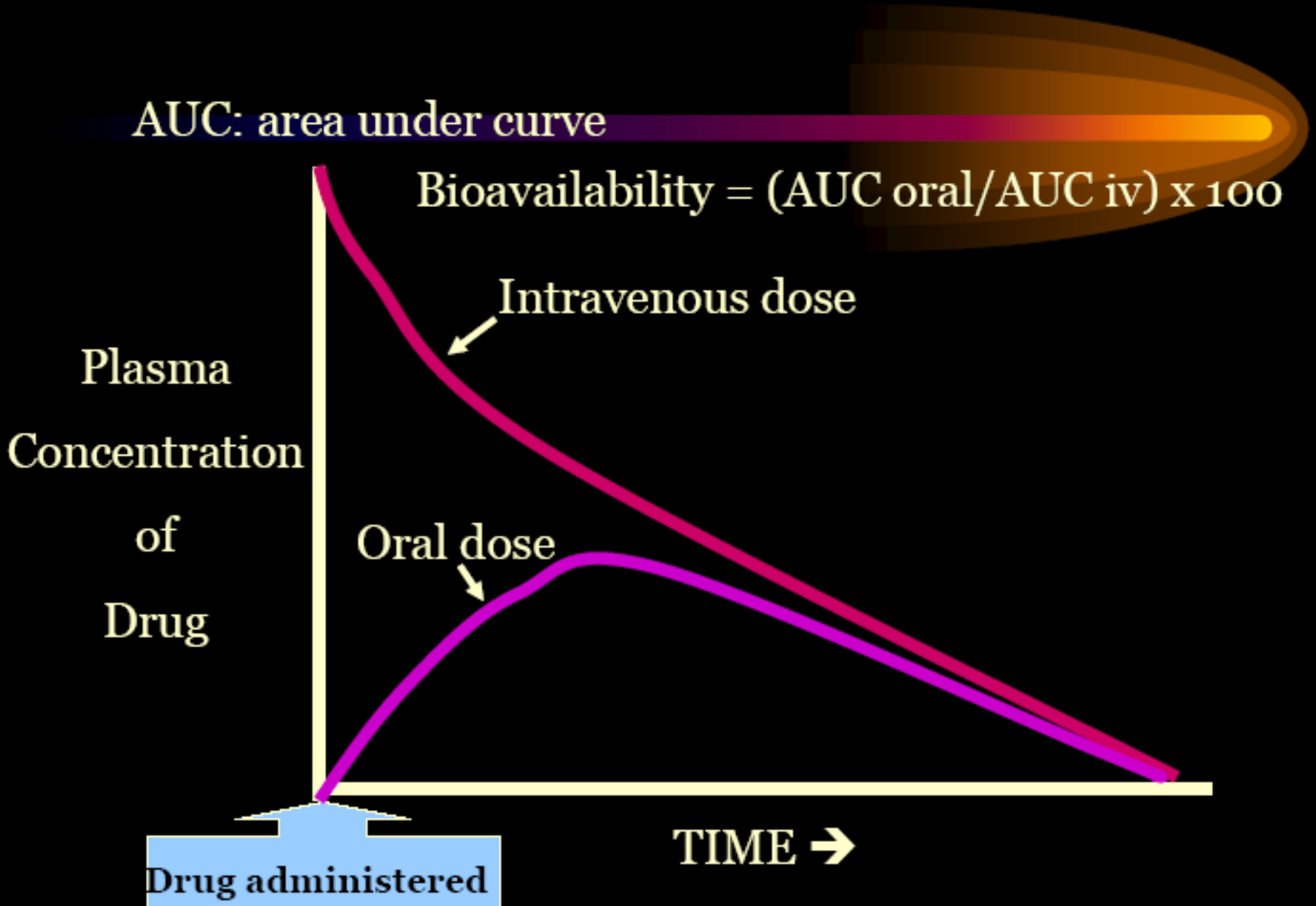
“The percentage of administered drug that reaches the systemic circulation in a chemically unchanged form”

- **Thus by definition a drug that is administered by intravenous route has 100% bioavailability**

Determination of Bioavailability

- We Compare plasma levels of a drug after different routes of administration with the plasma levels achieved by intravenous route (100% Bioavailability)

Plasma Drug Concentration Curve



Factors Affecting Bioavailability

- ***All factors affecting absorption of drugs through affect bioavailability***

- ***Especially Pharmaceutical Factors***

  The amount of drug that is released from a dosage form is highly dependent on its formulation

- **With tablets for example particle size, diluting substances and tablet size can affect disintegration and dissolution and thus bioavailability of the drug**
- **Manufactures should produce a formulation with unvaried bioavailability**

Table 3–3 Routes of Administration, Bioavailability, and General Characteristics.

Route	Bioavailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to ≤ 100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤ 100	Smaller volumes than IM; may be painful
Oral (PO)	5 to < 100	Most convenient; first-pass effect may be significant
Rectal (PR)	30 to < 100	Less first-pass effect than oral
Inhalation	5 to < 100	Often very rapid onset
Transdermal	80 to ≤ 100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

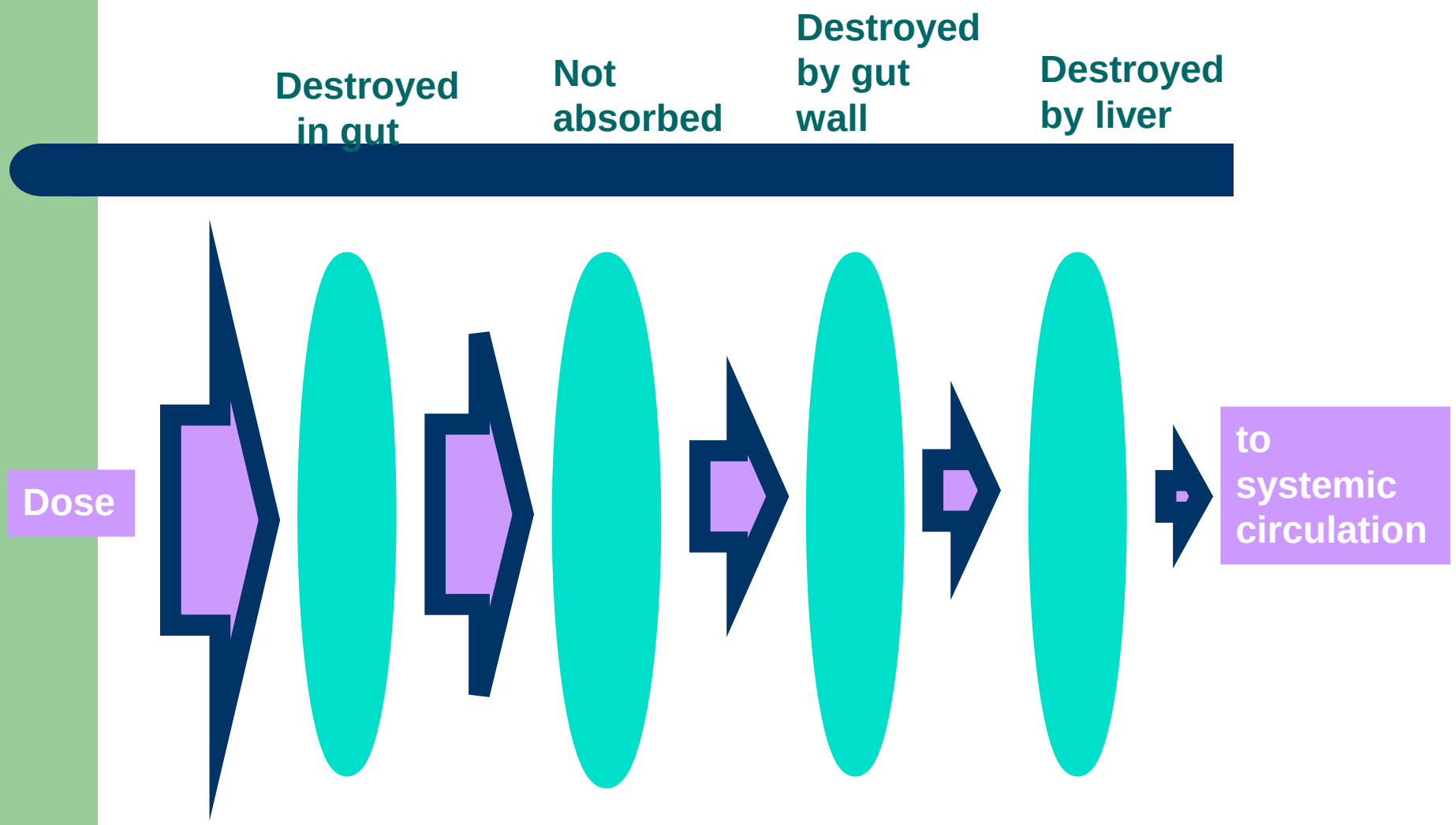
First Pass Metabolism

- **First Pass Effect/Presystemic Elimination**
- **Elimination of a drug before it reaches the systemic circulation**

- **Sites:**

  Wall of GIT and Mainly Liver, skin, lungs, etc

Bioavailability



- **If a drug is metabolized in the liver or excreted in the bile some of the active drug will be inactivated or diverted before it reaches the systemic circulation = decreased bioavailability**
- ***What about Rectal route?***

- **In liver disease first pass metabolism is decreased and bioavailability increases**

- **Thus First Pass Metabolism decreases Bioavailability**

Rate of Bioavailability

- Both rate and extent can influence the clinical effectiveness of a drug
- Rate of Bioavailability can be important for drugs given as a single dose
- Increased rate means drug reaches the target concentration earlier-more rapid action

Significance of Bioavailability

- Gives an estimation of the % of drug available for action
- Can Determine Route of Administration
- Determines Frequency of administration
- Same drug produced by different manufacturers can have different bioavailabilities

For drugs taken by routes other than the i.v. route, **bioavailability** must be understood in order to determine what dose will induce the desired therapeutic effect.

It will also explain why the same dose may cause a therapeutic effect by one route but a toxic or no effect by another.

Bioequivalence

Drugs are pharmaceutical equivalents if they contain the same active ingredients and are identical in dose (quantity of drug), dosage form (e.g., pill formulation), and route of administration.

Bioequivalence exists between two such products when the rates and extent of bioavailability of their active ingredient are not significantly different.

THE END.